In the Specification

Please replace the first and second section titles on page 1 and paragraph [0001] with the following:

Technical Field ~~to which the Invention Pertains~~

[0001] ~~The present invention~~ This disclosure relates to a process for producing an oxycarbonyl-substituted piperazine derivative by oxycarbonylating a piperazine derivative.

Background ~~Art~~

Please replace paragraph [0005] with the following:

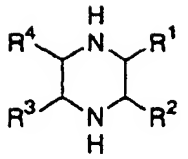
[0005] So, in the case where a water-soluble piperazine derivative is made to react by a generally publicly known method of a liquid-liquid two-phase system, the yield of the oxycarbonyl-substituted piperazine derivative is as low as less than 50%. It was found that the byproduct in which both the two nitrogen atoms of the piperazine provided as the raw material are substituted by oxycarbonyl groups is produced more than the intended oxycarbonyl-substituted piperazine derivative. Therefore, it is demanded to create a simple method for producing an oxycarbonyl-substituted piperazine derivative at a high yield. ~~The object of this inventtion is~~ It could therefore be advantageous to provide a process for producing an oxycarbonyl-substituted piperazine derivative at a high yield by oxycarbonylating a piperazine derivative.

Please replace the section title on page 3 and paragraphs [0006] and [0007] with the following:

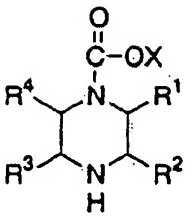
~~Disclosure of the Invention~~ Summary

~~[0006] The inventors studied intensively on the process for producing an oxycarbonyl-substituted piperazine derivative by oxycarbonylating a piperazine derivative, and completed the present invention.~~

[0007] ~~That is, this invention is~~ We provide a process for producing an oxycarbonyl-substituted piperazine derivative, in which a piperazine derivative represented by general formula (1) is oxycarbonylated to produce an oxycarbonyl-substituted piperazine derivative represented by general formula (2)



(1)



(2)

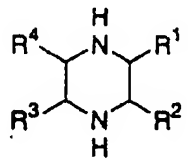
(where R^1, R^2, R^3 and R^4 denote, respectively independently, i) a hydrogen atom, ii) an alkyl group with 1 to 4 carbon atoms, iii) an alkoxy group with 1 to 4 carbon atoms, iv) a halogen group, v) a carboxyl group, vi) a carbamoyl group, or vii) an N-alkylcarbamoyl group with 1 to 4 carbon atoms in its alkyl group; X denotes i) an alkyl group with 1 to 4 carbon atoms, ii) an alkenyl group with 2 to 4 carbon atoms, iii) an alkynyl group with 2 to 4 carbon atoms, iv) an aralkyl group not substituted in the aromatic ring, or substituted by an alkyl group with 1 to 4 carbon atoms or by an alkoxy group with 1 to 4 carbon atoms or by a halogen group, or v) an aryl group not substituted in the aromatic ring, or substituted by an alkyl group with 1 to 4 carbon atoms or by an alkoxy group with 1 to 4 carbon atoms or by a halogen group; excluding the case where all of R^1, R^2, R^3 and R^4 denote a hydrogen atom respectively), characterized in that an organic solvent with a water content of 15 wt% or less is used. The oxycarbonyl-substituted piperazine derivative ~~in this invention~~ can also be a racemic modification or optically active substance.

Please replace the section title on page 5 and paragraph [0009] with the following:

~~The Best Modes for Carrying Out the Invention~~ Detailed Description

[0008] A particular method of this reaction will be exemplified.

[0009] The piperazine derivative represented by general formula (1) ~~and used in this invention~~



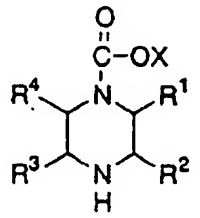
(1)

(where R^1, R^2, R^3 and R^4 denote, respectively independently, i) a hydrogen atom, ii) an alkyl group with 1 to 4 carbon atoms, iii) an alkoxy group with 1 to 4 carbon atoms, iv) a halogen group, v) a carboxyl group, vi) a carbamoyl group, or vii) an N-alkylcarbamoyl group with 1 to 4 carbon atoms

in its alkyl group; excluding the case where all of R^1, R^2, R^3 and R^4 denote a hydrogen atom respectively) is a piperazine derivative substituted by one to four substituent groups. Examples of it include 2-methylpiperazine, 2-ethylpiperazine, 2,3-dimethylpiperazine, 2-methoxypiperazine, 2-isopropoxypiperazine, 2-methoxy-5-n-butoxypiperazine, 2-chloropiper-azine, 2-bromopiperazine, 2,6-dichloropiperazine, 2-methyl-3-chloropiperazine, 2-piperadine-carboxylic acid, 2-ethyl-3-piperazinecarboxylic acid, 2-tert-butyl-3-piperazinecarboxylic acid, 2-piperazinecarboxamide, 2-ethyl-3-piperazinecarboxamide, 2-tert-butylcarboxamide, 3-methoxy-2-tert-butylcarboxamide, 2-n-butylcarboxamide, etc. Preferred are 2-methylpiperazine, 2-ethyl-piperazine and 2,3-dimethylpiperazine. More preferred is 2-methylpiperazine. Any of them can also be a racemic modification or optically active substance.

Please replace paragraph [0011] with the following:

[0011] ~~Now, the~~ The oxycarbonyl-substituted piperazine derivative obtained ~~in this invention~~ is represented by general formula (2):



(2)

(where R^1, R^2, R^3 and R^4 denote, respectively independently, i) a hydrogen atom, ii) an alkyl group with 1 to 4 carbon atoms, iii) an alkoxy group with 1 to 4 carbon atoms, iv) a halogen group, v) a carboxyl group, vi) a carbamoyl group, or vii) an N-alkylcarbamoyl group with 1 to 4 carbon atoms in its alkyl group; X denotes i) an alkyl group with 1 to 4 carbon atoms, ii) an alkenyl group with 2 to 4 carbon atoms, iii) an alkynyl group with 2 to 4 carbon atoms, iv) an aralkyl group not substituted in the aromatic ring, or substituted by an alkyl group with 1 to 4 carbon atoms or by an alkoxy group with 1 to 4 carbon atoms or by a halogen group, or v) an aryl group not substituted in the aromatic ring, or substituted by an alkyl group with 1 to 4 carbon atoms or by an alkoxy group with 1 to 4 carbon atoms or by a halogen group; excluding the case where all of R^1, R^2, R^3 and R^4 denote a hydrogen atom respectively), and it is preferred that X denotes a tert-butyl group or benzyl group. Examples include 1-methoxycarbonyl-2-methylpiperazine, 1-methoxycarbonyl-3-methylpiperazine,

2-ethyl-1-methoxycarbonylpiperazine, 1-ethoxycarbonyl-2-methylpiperazine, 1-tert-butoxycarbonyl-2-methylpiperazine, 1-tert-butoxycarbonyl-3-methylpiperazine, 1-tert-butoxycarbonyl-2,3-dimethylpiperazine, 1-tert-bu-toxycarbonyl-2-methoxy-3-methylpiperazine, 1-vinyloxycarbonylpiperazine, 1-vinyl-2-methylpiperazine, 1-vinyl-3-methylpiperazine, 1-allyloxycarbonylpiperazine, 1-allyloxycarbonyl-2-methylpiperazine, 1-allyloxycarbonyl-3-methylpiperazine, 1-methylpropionyloxycarbonyl-2-methylpiperazine, 1-benzyloxycarbonyl-2-piperazine, 1-benzyloxycarbonyl-3-methylpiperazine, 1-benzyloxycarbonyl-2,3-dimethylmethylpiperazine, 1-benzyloxycarbonyl-3,5-dimethylpiperazine, 1-benzyloxycarbonyl-3-methoxypiperazine, 1-(p-methylphenylmethyl)oxycarbonyl-2-methylpiperazine, 1-(p-methylphenylmethyl)oxycarbonyl-3-methylpiperazine, 1-phenoxy-carbonyl-2-methylpiperazine, 1-phenoxycarbonyl-2-methylpiperazine, 1-phenoxycarbonyl-3-methylpiperazine, 1-phenoxycarbonyl-2,5-dimethylpiperazine, etc. These compounds can be synthesized from general formula (1), and can be either racemic modifications or optically active substances.

Please replace paragraph [0018] with the following:

[0018] The water content ~~used in this invention~~ does not mean the rate of only the water homogeneously dissolved in the organic solvent, but means the rate of the water forming a two-phase system due to separation from the organic solvent. For example, in a water-toluene system, water-1-butanol system or the like, water can exist separately in the lower layer while the organic solvent can exist in the upper layer, and such a case is included. In this case, the water contents in the respective upper and lower layers can be individually measured, and the water content of the organic solvent can be calculated from the following calculation formula: (Water content of the organic solvent) = 100 x (Water content of the upper layer x Weight of the upper layer + Water content of the lower layer x Weight of the lower layer)/(Weight of the upper layer + Weight of the lower layer).

Please replace paragraph [0021] with the following:

[0021] Meanwhile, usually in oxycarbonylation, a basic compound is often added for capturing hydrochloric acid produced as a byproduct. Also ~~in this invention~~, the addition of a basic compound is an effective means. That is, a basic compound can be made to coexist in the reaction system when the piperazine derivative is oxycarbonylated.

Please replace paragraph [0024] with the following:

[0024] The reason why an aromatic nitrogen-containing compound is preferred ~~in this invention~~ is that it has a capability of activating an oxycarbonylating agent to a medium extent. That is, since an aromatic nitrogen-containing compound is weaker in basicity than an aliphatic nitrogen-containing compound typified by trimethylamine, it does not activate the oxycarbonylating agent excessively. So, it can be said that a side reaction to oxycarbonylate both the two nitrogen atoms of the piperazine derivative simultaneously is hard to occur.

Please replace paragraph [0036] with the following:

[0036] The piperazine derivative ~~used in this invention~~ can be used in any of various forms such as liquid or solid, and especially in the latter, any of various forms ranging from mass to pellets can be used. Even in the case where any of racemic piperazine derivative is made into an optically active substance by an optical resolution method, a piperazine derivative with either property of liquid or solid can be used. Furthermore, the piperazine derivative can be used in a free state or in a state of a salt with an optical resolving agent for the oxycarbonylation reaction.

Please replace paragraph [0038] with the following:

[0038] The amount of the optically active resolving agent used here is decided in reference to the mole balance between an acid and a base. Since the piperazine derivative ~~used in this invention~~ is a diacidic base, in the case where the optically active resolving agent is a dibasic acid, the amount of the optically active resolving agent used is usually from 0.1 to 1.5 molar times, preferably from 0.2 to 1.3 molar times, and more preferably from 0.3 to 1.2 molar times based on the amount of the piperazine derivative.

Please replace paragraph [0065] with the following:

[0065] On the other hand, it can be seen that in the case where the alkaline earth metal salt ~~of this invention~~ is used, the separation from the optically active piperazine derivative is easy.

Please replace paragraph [0092] with the following:

[0092] ~~The inventors precisely~~ We evaluated and analyzed the thermal stability of the oxycarbonyl-substituted piperazine derivative represented by the general formula (2), and as a result, found that the compound is partially thermally decomposed. That is, it was found that the oxycarbonyl group causes decarboxylation owing to heat. It was confirmed that the stability of the compound is greatly affected by the temperature and the heating time period.

Please replace paragraph [0103] with the following:

[0103] Irrespective of the distiller used, the distillation step can be performed, but it is preferred to use a thin film distiller. On a laboratory scale, the difference between both the distillers does not clearly appear, but in the case where distillation is performed on an industrial scale, it is considered that a thin film distiller is more advantageous. In this case, the distillate in the latter half of distillation is subject to a heat history of longer time. So, in the case of a thin film distiller, since the contact time with the heat source can be kept shortest, the temperature of the heat source can be raised compared with that of a batch distiller, it can be said to be more suitable for distillation of a thermally unstable compound with a high boiling point. Therefore, it can be said that a thin film distiller is suitable for the distillation of the oxycarbonyl-substituted piperazine derivative ~~in this invention~~. If the distillation step is performed, the impurities represented by the general formula (5) and the general formula (8), which could not be removed in the washing step, can be removed.

Please replace paragraph [0109] with the following:

[0109] ~~In this invention, the~~ The contents of the impurities represented by the general formulae (5) to (8) contained in the reaction solution containing the oxycarbonyl-substituted piperazine derivative can be obtained in reference to the total amount of the impurities represented by the general formula (5) to (8) and the oxycarbonyl-substituted piperazine derivative represented by the general formula (2), i.e., from the following calculation formula $\{(A2 + A3 + A4 + A5)/(A1 + A2 + A3 + A4 + A5) \times 100(\%)$, wherein A1, A2, A3, A4 and A5 respectively denote the area percentage of the oxycarbonyl-substituted piperazine derivative represented by the general formula (2), the area percentage of the impurity represented by the general formula (5), the area percentage of the impurity represented by the general formula (6), the area percentage of the impurity represented by the general formula (7)

and the area percentage of the impurity represented by the general formula (8). Similarly the contents of the respective impurities can be obtained.

Please replace paragraph [0112] with the following:

[0112] ~~This invention~~ The process is described below in detail in reference to examples, but is not limited thereto or thereby. In the following, benzyloxycarbonylation is briefly expressed as Z-protection, and tert-butoxycarbonylation, as Boc-protection.

Please replace paragraph [0116] with the following:

[0116] Furthermore, the reaction yield of 1-tert-butoxycarbonyl-3-methylpiperazine was calculated from (~~Said~~ the conversion x ~~Said~~ the selectivity)/100(%).

Please replace paragraph [0183] with the following:

Industrial Applicability

[0183] ~~According to this invention, an~~ An oxycarbonyl-substituted piperazine derivative can be produced at a high yield by oxycarbonylating a piperazine derivative under mild conditions using simple equipment.